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Reassessment of the Neural Control of Body Temperature: Importance of Oscillating Neural and Motor Components

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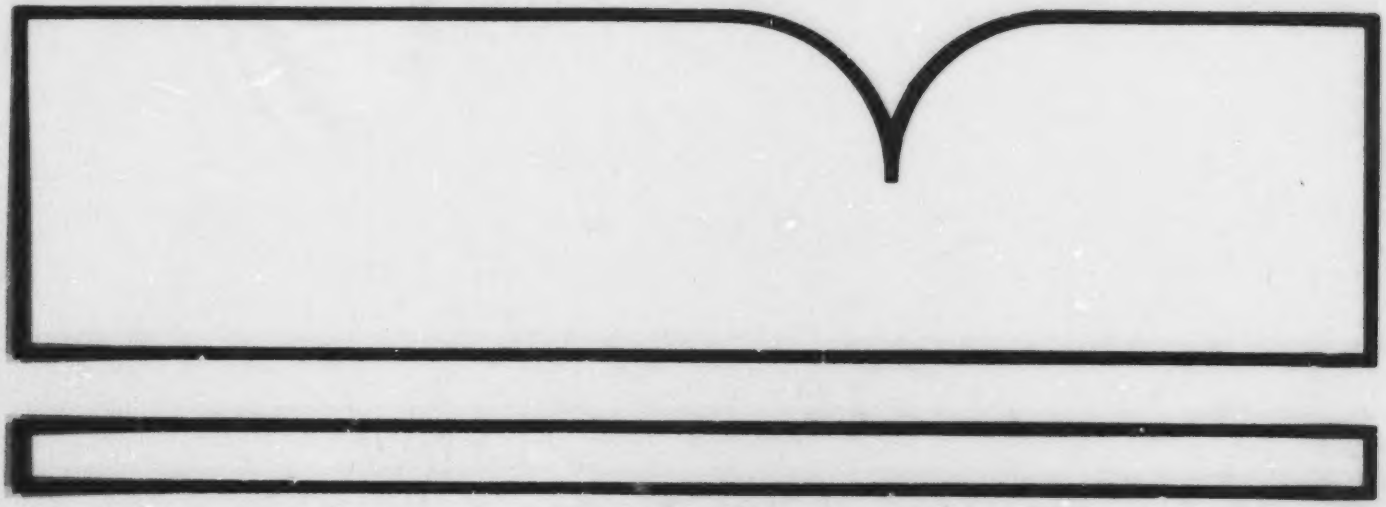

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16. ABSTRACT

1. Components in the sensory, integrative, and motor divisons of the thermoregulatory system exhibit rhythmic activity covering a frequency range over five orders of magnitude. In spite of these rhythmic properties, current models of thermoregulation are nonoscillatory. 2. The connectivity of the current neural models is empirically correct when applied to predicting changes in metabolism during central thermal and/or neurochemical stimulation. 3. However, because these models lack a temporal compensation, the operating principles of a thermoregulatory neural network remains unclear. 4. This paper presents strong evidence that integrative thermoregulatory neurons exert a variety of rhythmic control over all thermoregulatory motor outputs. 5. Furthermore, it is shown that without an oscillating integrative and motor system, especially pathways controlling peripheral heat loss, a thermoregulatory system is unstable. 6. The preponderant rhythmic activity in the thermoregulatory systems indicates that neural modeling of physiological regulation should be designed with oscillatory control.

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REVIEW

REASSESSMENT OF THE NEURAL CONTROL OF BODY TEMPERATURE: IMPORTANCE OF OSCILLATING NEURAL AND MOTOR COMPONENTS

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Abstract—1. Components in the sensory, integrative, and motor divisions of the thermoregulatory system exhibit rhythmic activity covering a frequency range over five orders of magnitude. In spite of these rhythmic properties, current models of thermoregulation are nonoscillatory.

2. The connectivity of the current neural models is empirically correct when applied to predicting changes in metabolism during central thermal and/or neurochemical stimulation.

3. However, because these models lack a temporal compensation, the operating principles of a thermoregulatory neural network remains unclear.

4. This paper presents strong evidence that integrative thermoregulatory neurons exert a variety of rhythmic control over all thermoregulatory motor outputs.

5. Furthermore, it is shown that without an oscillating integrative and motor system, especially pathways controlling peripheral heat loss, a thermoregulatory system is unstable.

6. The preponderant rhythmic activity in the thermoregulatory systems indicates that neural modelling of physiological regulation should be designed with oscillatory control.

INTRODUCTION

Over 40 years ago it was suggested that the thermoregulatory control center in the hypothalamus exerted a slow rhythmic control over peripheral heat loss (Burton, 1939). Measuring blood flow in the fingers of human subjects, Burton & Taylor (1940) found that, superimposed on the systolic–diastolic pulse, blood flow rhythmically oscillated with a skin temperature-dependent frequency ranging from 0.01 to 0.03 Hz. In one pathological case, a patient lacking rhythmic peripheral blood flow also had a poor ability to maintain normal body temperature under thermal stress.

The work of Burton has not been seriously considered in the current development of neural models describing the control of body temperature. Conventional research in temperature regulation has centered on the pharmacological (Bligh, 1973; Clark, 1979; Clark & Clark, 1980), electrophysiological (Hensel, 1974; Reaves & Hayward, 1979) and thermal sensitive properties (Crawshaw, 1980; Hammel, 1968; Satinoff, 1978) of the hypothalamus and other sites in the central nervous system (CNS). Two popular neural models for the control of body temperature have been developed (Fig. 1). It is important to note that these *neural* models were originally derived from studies measuring thermoregulatory responses (e.g. oxygen consumption, evaporative water loss and skin temperature) during thermal and/or chemical stimulation of the CNS. Because they are simple, these models have often been used for data interpretation in thermal physiological studies (Horowitz & Horwitz, 1979). However, the mechanism by which the depicted neurons control the thermoregulatory motor outputs for heat generation and dissipation is obscure.

Inspection of the literature reveals that physiologists have generally taken a "centripetal" approach to studying the neural basis of temperature regulation. That is, investigators who have recorded single units in the hypothalamus have tended to report the effects of temperature on neuron activity in a similar manner as was done in the thermoregulatory studies (Boulant & Bignall, 1973; Hellon, 1967, 1970, 1972) (e.g. graphing mean changes of single unit activity at various levels of hypothalamic and/or peripheral thermal stimulation). Since CNS neurons control motor output activity, it would be consistent to take a "centrifugal" approach to the study of the control of body temperature. In other words, previous studies have evaluated the neural activity in terms of the motor response rather than viewing the motor response in terms of the neural activity. In order to take a centrifugal approach it is necessary to closely scrutinize the temporal and spatial patterns of the sensory, integrative, and motor processes of the thermoregulatory system.

In spite of the immense amount of neurophysiological data collected in thermoregulation, we still do not know how the neural elements exert control over body temperature. We believe that the rhythmic hypothesis of Burton is a viable guide to the nature of the neural control of body temperature. This paper will (i) draw together evidence of the dominance of rhythmic processes in the sensory, integrative, motor components of temperature regulation, and (ii) will

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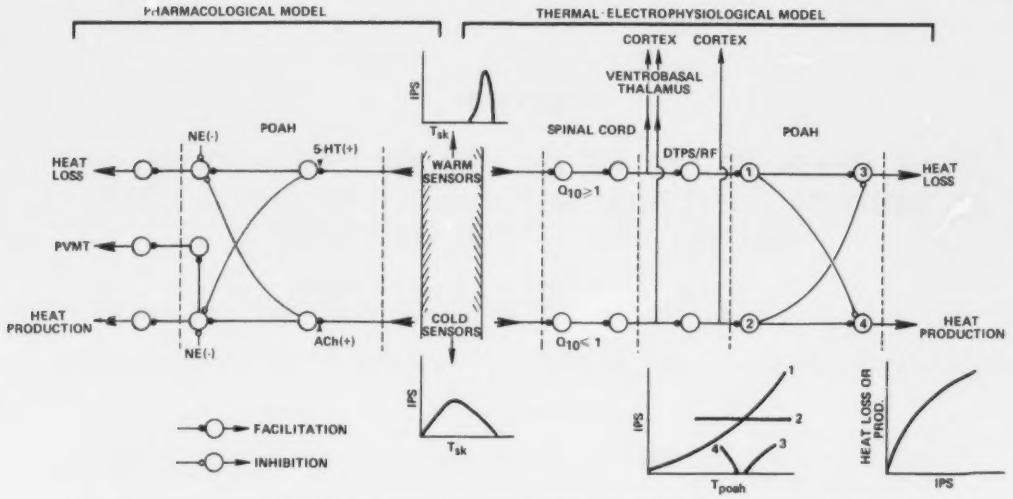


Fig. 1. Current neural models of temperature regulation based on response of mammals to pharmacological and thermal stimulation of the CNS. Firing rate (IPS) vs temperature profiles are given for the neurons in the thermal-electrophysiological model. Note that both models incorporate cross-inhibitory connections between the warm- and cold-sensitive pathways in the POAH. *Abbreviations*: NE—norepinepherine; 5-HT– 5-hydroxytryptamine; ACh—acetylcholine; PVMT—peripheral vasomotor tone; DTPS/RF—diffuse thalamic projection system/reticular formation. Pharmacological model from Bligh *et al.* (1973); thermal-electrophysiological model from Hammel *et al.* (1973).

analyze the spatial and temporal characteristics of these rhythmic elements in terms of modelling the central neural control of body temperature.

RHYTHMIC ELEMENTS OF THE THERMOREGULATORY SYSTEM

The neural and motor components of temperature regulation include a diversity of rhythmic processes which cover a frequency range of at least five orders of magnitude (Table 1). The frequency range of the thermoafferent system (peripheral thermoreceptors and ascending connectives in the brain and spinal cord) is relatively small (1–7 Hz), whereas the neural integrative and motor divisions exhibit oscillating activity ranging from 10^{-4} to 10 Hz. Many of the frequency calculations in Table 1 were not determined by the original authors. We have calculated many of the frequencies by analysis of the published analog data.

Motor division

Thermoregulatory motor outputs oscillate at frequencies as high as 18 Hz (shivering) and as low as 10^{-4} (cold-induced vasodilation). If one considers circadian, monthly (e.g. ovulation-induced peaks in body temperature), and circannual rhythms (e.g. hibernation), then the low frequency can be extended to 10^{-5}, 10^{-7} and 10^{-8} Hz, respectively.

Three major motor outputs, vasomotor control, shivering, and sweating, oscillate at a relatively high frequency and they are also modulated at much slower frequencies. For example, skin temperature oscillates at 10^{-2} Hz with an amplitude slightly less than 1°C (Burton, 1939; Burton & Taylor, 1940) (Fig. 2). The rapid oscillations in temperature are probably a reflection of similar fluctuations in arterial blood pressure and subsequently peripheral blood flow (Kronert & Pleshka, 1976; Wiersma & Adams, 1950). Slow oscillations in arterial blood pressure ranging in frequency from 0.01 to 0.08 Hz have been designated as third-order, or Mayer waves (Preiss & Polosa, 1974). The rapid skin temperature rhythm is modulated with a larger amplitude, but much lower frequency of 10^{-4} to 10^{-3} Hz (Harada, 1971). Burton & Taylor (1940) found that the rapid blood flow rhythm persisted when the subjects were immersed in a water bath, thus discounting the possibility that the oscillations were a result of periodic changes in skin temperature. In addition, it was shown that the rhythm frequency increased with skin cooling and that the interaction between frequency and skin temperature differed greatly between summer and winter acclimatized subjects. Because the contraction rate of isolated vascular smooth muscle normally increases with temperature (Wiederhielm, 1966), the rhythms in the intact organism, which are inversely temperature dependent, must have a central origin. Peripheral blood flow exhibits an *en masse* rhythmicity, meaning that pulsations in the hand are synchronous with pulsations in the feet (Burton, 1975). The rhythm is thought to be elicited from an oscillating activity of CNS vasomotor center(s) (Burton, 1975). Slow oscillations in arterial blood pressure (Mayer waves) are associated with similar rhythmic activity patterns in preganglionic sympathetic nerve fibers (Preiss & Polosa, 1974).

The much slower, but larger amplitude skin temperature rhythms may not be as directly linked to neural control. Relatively large, rhythmic changes in skin temperature seem associated with overall shifts in the sleep–wake cycle (Hammel *et al.*, 1963) and behavioral temperature regulation (Adair, 1977).

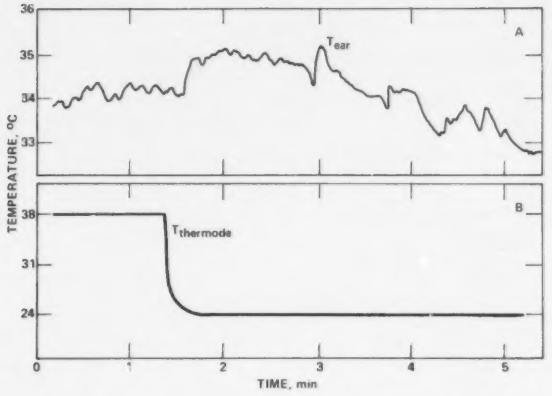


Fig. 2. Example of rhythmic fluctuations in ear skin temperature of a rabbit before and during POAH cooling. The temperature oscillations result in maximum warming and cooling rates of approx. 0.04–0.08 C/sec. $T_{thermode}$ = water temperature of a thermode implanted near the POAH. Note the desynchronization and slowing of the rhythm along with a reduction in ear temperature during POAH cooling. Cooling of the thermode to 24 C results in a 3 C drop in POAH temperature (from Gordon, 1980).

Cold-induced vasodilation, or the Lewis hunting response is one of the slowest rhythms in temperature regulation (10^{-4} Hz, Table 1). This motor response may have no neural control whatsoever, since the hunting response occurs in denervated as well as intact limbs (Schwinghamer & Adams, 1969).

The frequency of muscle contraction during shivering is the fastest rhythmic motor output in the thermoregulatory system (Table 1). Single unit activity of the motor neurons innervating a shivering muscle fire in synchronized bursts with the muscle contraction (Stuart *et al.*, 1966). Rhythmic shivering requires an intact spinal sensory-motor nerve connection and can be generated in spinal rather than supraspinal sites (Stuart *et al.*, 1963). The rapid muscle contractions may alternate in strong–weak cycles at a rate approx. 10–50 times slower than the primary rapid frequency of shivering (Burton & Edholm, 1955) (Table 1). This slow modulation of shivering occurs in cervically transected (Simon, 1974) as well as intact animals (Mott, 1963). Thus, the slow and rapid shivering rhythms can be generated in the spinal cord. It remains to be shown if supraspinal centers can modulate the slow shivering rhythm.

Eccrine sweat glands rhythmically pump fluid at a rate directly correlated with ambient temperature (Bini *et al.*, 1980; Ogawa & Asyama, 1978). The sweat expulsion rate may reach 0.25 Hz in very hot environments (Table 1). Using hygrophotographic recordings Nicolaidis & Sivadjian (1972) recorded pulsatile sweat discharge rates from individual eccrine glands with a frequency of 12 to 21 Hz. However, these very rapid sweating rates are apparently not synchronized with other sweat glands. Thus, the overall sweating rhythm does not exceed a frequency of 0.25 Hz. The relatively rapid sweating rhythm of ~0.25 Hz has been postulated to be a result of an oscillating tendency in a closed-loop sudomotor control system: a rise in skin temperature drives an outburst of sweat expulsion which lowers skin temperature causing an inhibition in sweating (Bini *et al.*, 1980).

When evaporative water loss is measured over a longer time interval, another sweating rhythm is apparent, but at a frequency approx. 30 times slower than the sweat gland expulsion rate (Randall & Hertzman, 1953). Bullard (1971) suggested that the slow oscillations in sweating may represent compensating adjustments by the temperature regulatory centers.

To briefly summarize, three important thermoregulatory motor outputs, sweating, shivering, and vasomotor tone cycle at relatively rapid rates with a small amplitude. These fast oscillations are modulated at frequencies that are 1–3 orders of magnitude slower but with a much larger amplitude. With few exceptions, the rhythmic processes have a direct neural origin. An understanding of the temporal characteristics of the motor outputs appears essential to assessing the operation of the neural control of temperature regulation.

Neural division

Activity of neurons in the peripheral and central nervous systems may oscillate at frequencies of 0.06–18 Hz (Table 1). The grouping of action potentials into bursts is a common property of cold thermoreceptors (Hensel, 1976; Iggo, 1969; Iggo & Young, 1975). At warm skin temperatures, the firing pattern of cold receptors is uniform and relatively slow. Reducing skin temperature increases the overall receptor firing rate concomitant with bursts alternated with silent periods. As skin cooling progresses, the number of spikes per burst increases, and the bursting frequency may be as high as 6 Hz (Table 1). Warm receptors generally do not exhibit bursting patterns during thermal stimulation (Darian-Smith *et al.*, 1979) although there are a few exceptions (Duclaux & Kenshalo, 1980).

In addition to the primary neurons of the thermoafferent system, peripheral thermal stimulation also promotes bursting of spikes in some neurons of the cortex (Hellon & Mitchell, 1975; Landgren, 1957),

Table 1. Examples of rhythmic processes in the neural and motor divisions of the thermoregulatory system

Species and condition	Parameter	Frequency (Hz)	Reference
Cold-exposed cat	hind limb shivering	18	Stuart *et al.* (1966)
Unanes. guinea pig during spinal thermal stimulation	EEG of POAH	10–18	Wünnenberg (1973)
Unanes. rabbit under thermoneutral conditions	POAH single unit activity	0.2–8.0	Gordon (1980)
Cold-exposed cat	hind limb shivering	7	Perkins (1945)
T_{sk} of monkey at 40 C	warm receptor unit bursting activity	7	Duclaux & Kenshalo (1980)
Low T_{sk} of monkey	cold receptor bursting activity	2–6	Poulos (1975)
Cooling of rat tongue	cold receptor bursting activity	5	Bade *et al.* (1970)
Cooling of peripheral sites in several species	cold receptor bursting activity	cat—5 rat—3 monkey—1	Hensel (1976)
Hyperthermia in humans	cortical EEG	0.5–3.0	Dubois *et al.* (1980)
Unanes. rabbit under thermoneutral conditions	posterior hypothalamic unit activity	1–3	Chernova *et al.* (1978)
Warming of rat scrotum	cortical neuron bursting activity	0.74–2.6	Hellon & Mitchell (1975)
Cooling of rat scrotum	cold receptor bursting activity	2.3	Hellon *et al.* (1975)
Low-decerebrated monkey	quadricep EMG shivering	1.2	Liu (1979)
Unanes. rabbit under thermoneutral conditions	POAH unit activity	2.2	Reaves (1976)
Anes. rabbit during hypothalamic heating	EEG of hippocampus	1.1 to desync. with heating	Von Euler & Soderberg (1957)
Cold-exposed cat	hind limb shivering	0.38–1.0	Perkins (1945) Stuart *et al.* (1966)
Cooling of rat scrotum	cold receptor bursting activity	0.72	Pierau *et al.* (1975)
Anes. cat under thermoneutral conditions	bursting activity of sympathetic post-gangelionic fiber	0.5	Horeyseck *et al.* (1976)
Human at 18–38 C	sympathetic vasoconstriction nerve activity	0.08–0.5*	Bini *et al.* (1980)
Spinal cooling of rabbit	regional sympathetic activity of post-ganglionic nerve fibers	0.35	Iriki *et al.* (1971) Walther *et al.* (1980)
Cooling of cat tongue	cortical neuron bursting activity	0.35	Landgren (1957)
Semi-nude, heat stressed human	forearm sweating	0.25	Bini *et al.* (1980) Ogawa & Asyama (1978)
Cold-exposed cat with severed carotid sinus & right aortic nerves	EMG of acromiotrapezium muscle	0.16	Little *et al.* (1980)
Rabbit at 22 C	ear T_{sk}	0.10	Gordon (1980) (cf. Fig. 2)
Cold-exposed human	EMG	0.10	Burton & Edholm (1955)
Midsection cooling of rabbit	hind limb EMG	0.09	Mott (1963)
Cervical-transected dog during spinal cooling	hind limb EMG	0.06–0.08	Simon (1974)
POAH thermal stimulation in rabbit	POAH unit activity	0.067	Gordon & Heath (1980)
External heat loaded dog	lingual arterial blood flow	0.064	Krönert & Pleschka (1976)
Hypothalamic thermal stimulation in rabbit	hypothalamic DC potential	0.05	Von Euler (1980)
POAH cooling in goat	POAH cold-sensitive unit activity	0.02–0.03	Mercer *et al.* (1978)
Humans in water bath	finger blood flow	0.014–0.033*	Burton (1939) Burton & Taylor (1940)
Partial cooling of rabbit ears	T_{sk} directly over artery	0.016–0.02	Udeu (1978)
Warming of rat scrotum	thalamic unit activity	0.009 at 35 C 1–2 at 29 C	Jahns (1975)

Table 1. (*Continued*)

Species and condition	Parameter	Frequency (Hz)	Reference
Heat stressed humans	EWL from dorsum of foot	0.008	Randall & Hertzman (1953)
Sheep exposed to −10°C	ear T_{sk}	0.0016	Bianca (1967)
Rabbit at 5°C	metabolic rate	0.001	Gonzalez *et al.* (1971)
Humans at rest	metabolic rate	0.0001–0.0003	Bailey *et al.* (1973)
Foot of monkey in ice bath	foot T_{sk}	0.0008–0.001	Mathew *et al.* (1978)
Human finger in ice bath	finger T_{sk}	0.0004	Keatinge (1969)
Rabbit at −5 to −30°C	ear T_{sk}	0.0002–0.001 max at 20°C min at 0°C	Harada (1971)

Abbreviations: EMG—electromyogram; EEG—electroencephalogram; T_{sk}—skin temperature; POAH—preoptic/anterior hypothalamus; EWL—evaporative water loss; anes.—anesthetized; unanes.—unanesthetized.
*Frequency increased with decreasing temperature.

thalamus (Jahns, 1975; Schingnitz & Werner, 1980), posterior hypothalamus (Chernova *et al.*, 1978) and POAH area (Gordon & Heath, 1981; Reaves & Heath, 1975). A warm-responsive thalamic neuron in the rat exhibited two different forms of rhythmic activity (Jahns, 1975): an extremely slow pattern at 0.009 Hz occurred at a skin temperature of 35°C and a rapid bursting pattern of 1–2 Hz at 29°C. The fact that bursting patterns of similar frequency occur in primary as well as integrative CNS thermoregulatory neurons suggests that either the burst code of thermoreceptors is conveyed into the CNS and/or that CNS neurons are capable of generating an endogenous burst code. Low frequency modulation of a relatively rapid bursting activity, as occurs in the motor systems, has apparently not been investigated in the nervous system.

Bursting and information transfer in the CNS

Nerve–nerve and nerve–muscle synapses can be viewed as equivalent to low-pass electronic filters (McKean *et al.*, 1970; Terzuolo & Bayly, 1968). If the modulation frequency of a spike train (e.g. burst frequency, Fig. 3) exceeds the cut-off frequency of the synapse, then the gain of information transfer [e.g. $\simeq 20 \log_{10}$ (Δ firing rate of postsynaptic neuron/Δ firing rate presynaptic neuron)] will decrease. The cut-off frequency of the synapse is dependent on the voltage decay time of the postsynaptic membrane and other cytoarchitectural complexities. Thus, a series of synaptic junctions with varying cut-off frequencies can selectively pass certain bursting presynaptic spike trains over others.

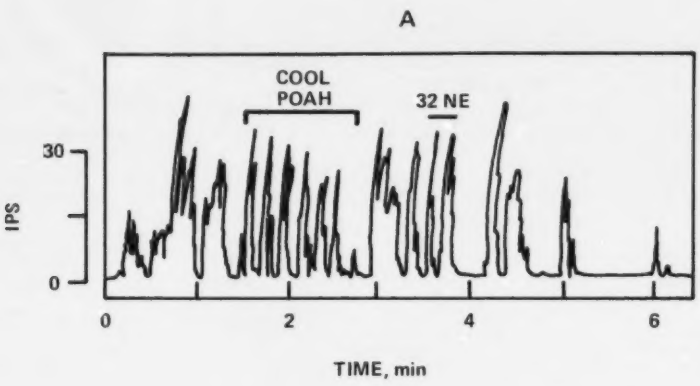
Variation in interspike intervals of a spike train is considered a likely coding mechanism in the nervous system (Perkel & Bullock, 1968). Initial experiments with invertebrates demonstrated that neuromuscular and ganglion cell junctions are highly sensitive to the pattern rather than absolute level of firing rate (Wiersma & Adams, 1950). Work in the mammalian CNS has demonstrated that variations in interspike intervals of a spike train are useful for sensory discrimination in the thalamus (Werner & Mountcastle, 1963) and cortex (Whitsel *et al.*, 1977). Thus, grouping spikes into bursts may be an important code for both transducing changes in temperature and conveying information from the sensory to integrative to motor pathways (Gordon & Heath, 1981; Jahns, 1975; Reaves & Heath, 1975; Schingnitz & Werner, 1980).

RHYTHM GENERATOR: SINGLE PACEMAKER OR NERVE NETWORK?

The neural parameters listed in Table 1 demonstrate that thermoregulatory neurons exhibit oscillatory activity with a frequency of 0.06–8.0 Hz. Some of the fastest rhythms are generated by warm and cold thermoreceptors. Since these primary neurons apparently have no presynaptic connectives, it can be concluded that thermoreceptors are pure pacemaker neurons. That is, they are capable of generating their own rhythmic activity without the aid of other neural inputs. On the other hand, extremely slow bursting activity (*ca* < 1.0 Hz) may have a more complex origin.

Electrophysiological studies of invertebrate nervous systems have provided much information on the generation of slow bursting activity (Bullock, 1977). Slow rhythmic motor outputs of invertebrates, such as feeding and locomotion, in many cases can be traced to the activity of single pacemaker cells which require no other synaptic input to generate oscillating spike trains. There is some evidence that slow oscillating neurons in the supraoptic nucleus generate pacemaker potentials (Haller, 1978). Contrary to a single cell hypothesis, a complex nerve network may be involved in generating an array of rhythmic activities. It is also possible to generate oscillatory neural activity with reciprocally inhibited, tonically active neurons (Perkel & Mulloney, 1974).

Recent neuropharmacological studies in the POAH imply that a network of thermal-sensitive and insensitive neurons is involved in the generation of slow rhythmic neural activity. Recording single unit activity in the unanesthetized rabbit, Gordon & Heath (1980) found several types of slow bursting neurons: tonically firing units that underwent slow bursting activity during POAH thermal stimulation, tonic units induced into bursting by local injections of norepinephrine (NE) or 5-hydroxytryptamine (5-HT), and



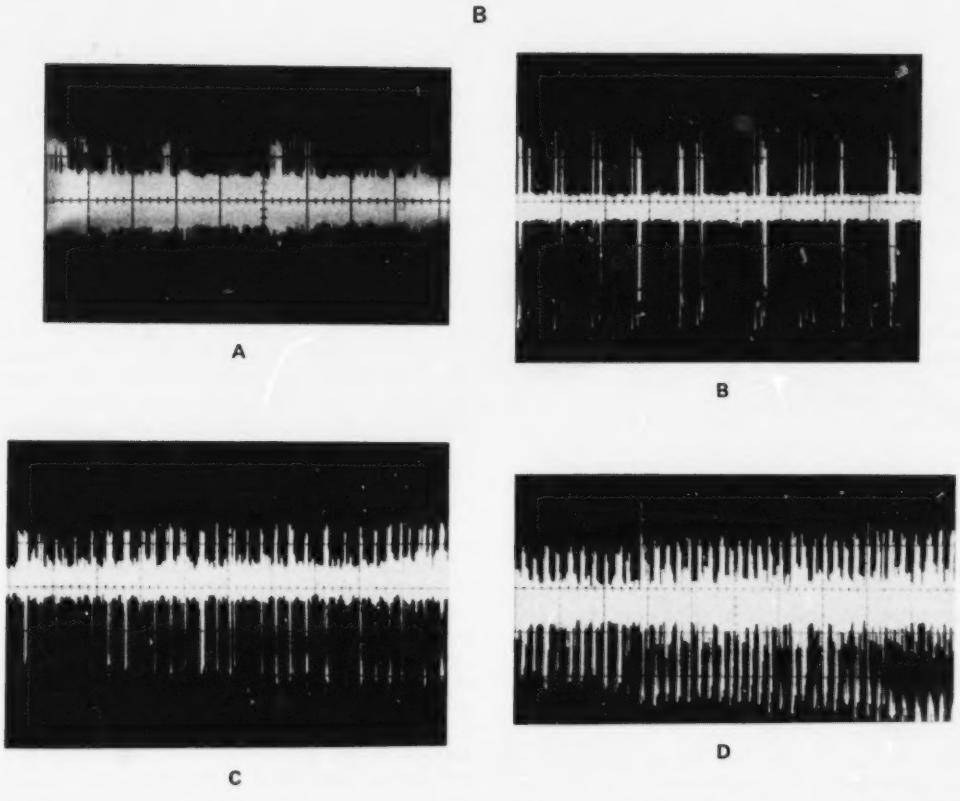


Fig. 3.(A) Example of a slow bursting neuron (~0.037 Hz) that underwent an increase in bursting (~0.08 Hz) during POAH cooling in the unanesthetized rabbit. An intraventricular injection of 32 μg of norepinephrine (NE) caused an inhibition of unit activity. ips—impulses/second (from Gordon, 1980; Gordon & Heath, 1980).

Fig. 3.(B) Examples of frequency modulated spike trains recorded in the POAH of unanesthetized rabbits under thermoneutral conditions. Approximate modulation frequency and calibration mark for trace A = 0.2 Hz, 4000 msec; trace B = 1.0 Hz, 1000 msec; trace C = 5.6 Hz, 1000 msec; and trace D = 8.0 Hz, 1000 msec.

thermal-induced bursting units that could have the bursting blocked with combinations of 5-HT, NE, and thermal stimulation (Fig. 3). The fact that bursting is dependent on combinations of thermal and chemical stimulation is evidence that a network of POAH neurons is involved in generating slow rhythmic activity.

MAINTENANCE OF STABILITY WITH AN OSCILLATING MOTOR OUTPUT

Potential of positive feedback in the control of skin temperature

Over 25 years ago it was recognized that the neural connectivity of the sensory-to-integrative-to-motor pathway for the control of nonevaporative heat loss from the skin is predictably a positive feedback system (Hardy, 1972; Hensel, 1952). The positive loop was predicted when skin cooling excited cold receptors which activated the vasomotor center to elicit peripheral vasoconstriction which then promoted further skin cooling. In spite of these observations, there are few if any prospects to explain how the control system "frees itself" from positive feedback.

The fact that the current neural models have no compensation for time response may lead one to predict that the system is susceptible to positive feedback. For example, the models of Fig. 1 imply that an increase in activity of a cutaneous warm-receptor causes an immediate activation of heat dissipating motor neurons and, at the same time, an inhibition of thermogenic motor neurons. Thus, they are "hard-wired" models, being similar to a monosynaptic spinal reflex. Although the designers of these models may not have intended an interpretation of such rapid neural responses, the absence of specified neural time constants leaves one with the only conclusion that the system's response is instantaneous. If animals employed a hard-wired network for regulating a system as complex as thermoregulation (see below), their body temperature could, under certain ambient conditions, become unstable.

The utility of an oscillating controlled system, such as the control of skin temperature, can best be illustrated by analyzing a theoretical thermoregulatory system with no oscillations (Fig. 4). For example, a brief period of skin cooling would be expected to increase the activity of cutaneous cold-receptors which then activate POAH cold-sensitive neurons and finally, lead to peripheral vasoconstriction, which in turn is sensed as further cooling. A cycle of positive feedback is predicted in this arrangement: vasoconstriction leads to a reduction in skin temperature, which further activates cold receptors, which increases cold-sensitive and inhibits warm-sensitive POAH neurons, and hence, more vasoconstriction. A type of "runaway" vasoconstriction develops causing an increase in deep body temperature and is reversed only when POAH temperature surpasses the threshold for the activation of heat dissipatory motor outputs such as peripheral vasodilation. Then, as skin temperature increases and core temperature is reduced, a predicted "runaway" vasodilation would occur and is reversed only when core temperature is lowered to the point that thermogenic motor outputs activate resulting in vasoconstriction and thus skin cooling which leads to the start of another cooling cycle.

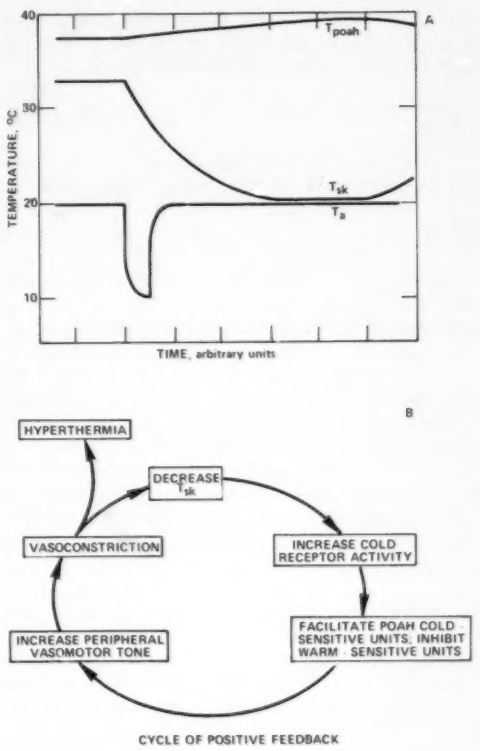


Fig. 4.(A) Predicted response of skin temperature (T_{sk}) based on models of Fig. 1, following a brief period of cooling. A reduction in ambient temperature (T_a) stimulates a positive feedback network as depicted in (B). The reduction in peripheral heat loss results in an elevation in body and brain (T_{POAH}) temperature which, in turn, stimulates warm-sensitive neurons in the POAH and elsewhere in the CNS resulting in an inhibition of the vasoconstriction response.

The overall effect predicted by the arrangement of the neural connectivity in Fig. 1 is a positively reinforced control of skin temperature which influences the level of core temperature. Because of thermal-sensitive neurons located in the POAH and elsewhere in the CNS, "runaway" vasoconstriction or vasodilation would not cause core temperature to reach a lethal level. As the current neural models are now depicted, one would predict that thermoregulation is accompanied with relatively large oscillations in skin and core temperature with the latter parameter lagging behind the former as depicted in Fig. 4. Of course, the mammalian thermoregulatory system exhibits much more stability than described by the foregoing analysis and does not normally undergo such "one-sided" changes in skin and core temperature.

The temperature response in Fig. 4 is an idealistic situation of what would occur with the neural model in Fig. 1 operative with no additional inputs. A principal point to now consider is, with the connectivity we know that exists between sensory, integrative, and

motor neurons, how can thermal homeostasis be achieved while, at the same time, avoiding a positive feedback loop as described above?

Avoiding positive feedback with an oscillating motor system

A problem with the models in Fig. 1, as they pertain to the control of skin temperature, is that the motor system dominates the activity of the sensory system. That is, the skin is packed with warm and cold temperature sensors and, through changes in its temperature, the skin is also the major site for the control of heat gain and loss. It is also important to note that cutaneous thermal receptors provide an accurate estimate of ambient temperature (i.e. degree to which animal gains or loses heat to/from the environment) only when the animal is maximally vasoconstricted. Cutaneous blood flow causes skin temperature to lie somewhere between the true ambient temperature and deep body temperature (e.g. decrease in blood flow causes skin temperature to approach ambient temperature, raising blood flow causes skin temperatures to approach deep core temperature). The temperature of the cutaneous thermal receptors is certainly related to ambient temperature but is also highly influenced by cutaneous blood flow. It is therefore evident that if the organism uses thermal receptors as a means of measuring ambient temperature then the CNS processing of the receptor information must be continually compensated by the degree of peripheral blood flow.

In our opinion, it is not possible for the sensory and motor systems, in their side-by-side spatial arrangement, to work simultaneously. An oscillating motor output temporally disassociates the sensory from the motor systems and therefore permits the skin to both sense ambient temperature and control heat loss. For example, in the case of the positive feed-back enforced vasoconstriction depicted in Fig. 4, rhythmic periods of vasodilation allow the cutaneous thermal receptors to evaluate the actual environmental temperature. The rate of sensory evaluation of environmental temperature is dependent on the oscillating frequency of the motor system. For example, a 0.1 Hz rhythm in skin temperature implies that the thermal receptors can "test" the ambient temperature every 10 sec.

This paper has demonstrated that the vasomotor system does oscillate; however, can the resulting skin temperature rhythms generate adequate stimuli to be processed in the CNS? 10^{-2} to 10^{-1} Hz oscillations in peripheral blood flow generate sinusoidal temperature ramps (i.e. $\Delta T_{sk}/\Delta$ time; Fig. 2) in the skin with slopes that are dependent on ambient temperature. It is well known that thermal receptors are extremely sensitive to relatively small, dynamic shifts in temperature rather than to static differences (Cabanac, 1975; Darian-Smith *et al.*, 1979; Hensel, 1974, 1976). At a 50% probability level, the threshold for the perception of warmth ranges between +0.001 and 0.002 C/sec, while the threshold for cold occurs between −0.005 and −0.006 C/sec (Hendler *et al.*, 1963). Recording unit activity in the caudal trigeminal nucleus of the cat, Dostrovsky & Hellon (1978) found that a thermal-responsive unit was sensitive to spontaneous 0.5 C changes in skin temperature (0.08–0.13°C/sec). Hence, it is likely that the rhythmic temperature ramps generated by an oscillating skin temperature are sufficient in magnitude to be transduced by both warm and cold thermosensors.

CONCLUSIONS AND SUMMARY

The current neural models of temperature regulation are empirically correct (Fig. 1). The modelled neurons are thought to be linear or logarithmic transducers that convert temperature to a change in firing rate. Past studies have recorded neuron activity with transducer properties similar to the neurons modelled in Fig. 1.

Bursting frequencies tend to be faster in the sensory division of the thermoregulatory system when compared to the integrative and motor divisions. Rhythmic spike trains in the sensory and integrative divisions may be necessary in a control system that employs synaptic junctions with varying low-pass frequency characteristics.

All thermoregulatory motor outputs, including skin temperature, sweating, shivering, and metabolism exhibit at least one frequency of rhythmic activity. Much of this paper has been devoted to analyzing the importance of a rhythmic skin temperature. Presently, it is unclear as to the functional importance of slow oscillations in the other motor outputs. With the array of rhythmic neuron activity in the integrative division of thermoregulatory control, it is not surprising to see some form of oscillation in all motor outputs.

Correlating the effects of temperature with both the neuron firing patterns and activity of heat generation/dissipation outputs will define the operating characteristics of the neural network, but only if the time interval used to assess activity is considerably less than the system's period of oscillation. We are suggesting that fundamental rhythmic properties incorporated into temperature regulation have been ignored because the motor studies, which have been extensively used for the design of neurophysiological experiments, have been inclined to present data averaged over intervals that are magnitudes longer than the peak-to-peak time of the rhythmic process. Hence, the oscillating motor outputs have been observed, but largely overlooked, perhaps for the sake of minimizing variation in the data. Incorporating rhythmicity into neural models of temperature regulation increases the stability of the models and more closely approximates a living system tested under a variety of thermal conditions.

The significance of oscillations in physiological control may have been best stated by Burton & Taylor (1940): "Integration with respect to time may be as important a property of nervous mechanisms as spatial integration, for it makes possible the effective regulation of a physiological phenomenon which is by nature continually fluctuating." In other words, in order to maintain a stable body temperature under conditions of irregular changes in ambient temperature, the nervous system must have the capacity to integrate the intrinsically rhythmic characteristics of thermoregulatory effectors (e.g. shivering, blood flow, and sweating). Proper integration of the rhythmic motor outputs result in a time-averaged steady state

intensity of an effector which leads to an overall regulation of skin and body temperature.

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REFERENCES

ADAIR E. R. (1977) Skin, preoptic, and core temperatures influence behavioral temperature regulation. *J. appl. Physiol.* **42,** 559–564.

BADE H., BRAUN H. A. & HENSEL H. (1979) Parameters of the static burst discharge of lingual cold receptors in the cat. *Pflugers Arch. ges. Physiol.* **382,** 1–5.

BAILEY D., HARRY D., JOHNSON R. E. & KUPPRAT I. (1973) Oscillations in oxygen consumption of man at rest. *J. appl. Physiol.* **34,** 467–470.

BIANCA W. (1967) The impact of the atmospheric environment on the integument of domestic animals. In *Biometeorology*, Vol. 3 (Edited by TROMP W. W. & WHITE W. H.), pp. 83–102. Swets & Zeitlinger, Amsterdam.

BINI G., HAGBARTH K., HYNNINEN P. & WALLIN B. G. (1980) Thermoregulatory and rhythm-generating mechanisms governing the sudomotor and vasoconstrictor outflow in human cutaneous nerves. *J. Physiol.* **306,** 537–552.

BLIGH J. (1973) Temperature regulation in mammals and other vertebrates. In *Frontiers of Biology*, Vol. 30 (Edited by NEUBERGER A. & TATUS E. L.). North-Holland, Amsterdam.

BLIGH J., SILVER A. & SMITH C. A. (1979) A central excitatory serotonergic or serotonergic-like synapse on the pathway to heat production in the sheep. *J. therm. Biol.* **4,** 259–268.

BOULANT J. A. & BIGNAL L. K. E. (1973) Change in thermosensitive characteristics of hypothalamic units over time. *Am. J. Physiol.* **225,** 311–318.

BULLARD R. W. (1971) Temperature regulation. In *Physiology* (Edited by SELKURT E. E.), pp. 651–667. Little, Brown, Boston.

BULLOCK T. (1977) *Introduction to Nervous Systems*. W. H. Freeman, San Francisco.

BURTON A. C. (1939) The range and variability of the blood flow in the human fingers and the vasomotor regulation of body temperature. *Am. J. Physiol.* **127,** 437–453.

BURTON A. C. & TAYLOR R. M. (1940) A study of the adjustment of peripheral vascular tone to the requirements of the regulation of body temperature. *Am. J. Physiol.* **129,** 565–577.

BURTON A. C. & EDHOLM O. G. (1955) *Man in a Cold Environment*. Edward Arnold, London.

BURTON A. C. (1975) *Physiology and Biophysics of the Circulation*, pp. 201–210. Year Book Medical Publishers, Chicago.

CABANAC M. (1975) Temperature regulation. *Ann. Rev. Physiol.* **38,** 415–439.

CHERNOVA N. D., DYMNIKOVA L. P. & KUSHAKOV D. (1978) Statistical investigation of the effect of local temperature changes on posterior hypothalamic single unit activity. *Neurophysiology* **10,** 262–267.

CLARK W. G. (1979) Changes in body temperature after administration of amino acids, peptides, dopamine, neuroleptics, and related agents. *Neurosci. Biobehav. Rev.* **3,** 179–231.

CLARK W. G. & CLARK Y. L. (1980) Changes in body temperature after administration of adrenergic and serotonergic agents and related drugs including antidepressants. *Neurosci. Biobehav. Rev.* **4,** 281–375.

CRAWSHAW L. I. (1980) Temperature regulation in vertebrates. *Ann. Rev. Physiol.* **42,** 473–491.

DARIAN-SMITH I., JOHNSON K. O., LAMOTTE C., SHIGENAGA Y., KENINS P. & CHAMPNESS P. (1979) Warm fibers innervating palmer and digital skin of the monkey: responses to thermal stimuli. *J. Neurophys.* **42,** 1297–1315.

DOSTROVSKY J. O. & HELLON R. F. (1978) The representation of facial temperature in the caudal trigeminal nucleus of the cat. *J. Physiol.* **277,** 29–47.

DUBOIS M., SATO S., LEES D. E., BULL J. M., SMITH R., WHITE B. G., MOORE H. & MACNAMARA T. E. (1980) Electroencephalographic changes during whole body hyperthermia in humans. *EEG & Clin. Neurophysiol.* **50,** 486–495.

DUCLAUX R. & KENSHALO D. R. (1980) Response characteristics of cutaneous warm receptors in the monkey. *J. Neurophysiol.* **43,** 1–15.

DYKES R. W. (1975) Coding of steady and transient temperatures by cutaneous "cold" fibers serving the hand of monkeys. *Brain Res.* **98,** 485–500.

GONZALEZ R. R., KLUGER M. J. & HARDY J. D. (1971) Partitional calorimetry of the New Zealand white rabbit at temperatures of 5–35°C. *J. appl. Physiol.* **31,** 728–734.

GORDON C. J. (1980) Neural mechanisms of thermoregulation in the rabbit, *Oryctolagus cuniculus*. Ph.D. Dissertation, Univ. Illinois, Urbana.

GORDON C. J. & HEATH J. E. (1980) Slow bursting thermal sensitive neurons in the preoptic area of the rabbit. *Brain Res. Bull.* **5,** 515–518.

GORDON C. J. & HEATH J. E. (1981) Temporal patterning of neuronal activity during thermal and neurochemical stimulation of the preoptic/anterior hypothalamus of the awake rabbit. *Neuropharmacology* **20,** 163–168.

HALLER E. W., BRIMBLE M. J. & WAKERLEY J. B. (1978) Phasic discharge in supraoptic neurones recorded from hypothalamic slices. *Exp. Brain Res.* **33,** 131–134.

HAMMEL H. T., JACKSON D. C., STOLWIJK J. A., HARDY J. D. & STROMME S. B. (1963) Temperature regulation by hypothalamic proportional control with an adjustable set point. *J. appl. Physiol.* **18,** 1146–1154.

HAMMEL H. T. (1968) Regulation of internal body temperature. *Ann. Rev. Physiol.* **30,** 641–710.

HAMMEL H. T., HELLER H. C. & SHARP F. R. (1973) Probing the rostral brainstem of anesthetized and unanesthetized, and exercising dogs and of hibernating and euthermic ground squirrels. *Fedn Proc. Fedn Am. Socs. exp. Biol.* **32**(5), 1588–1597.

HARADA E. (1971) A characteristic pattern of fluctuation in the skin temperature of the rabbit's ear in response to alteration of the environmental temperature. *J. Physiol. Soc. Jap.* **33,** 303–316.

HARDY J. D. (1972) Models of temperature regulation—a review. In *Essays on Temperature Regulation* (Edited by BLIGH J. & MOORE R. E.), pp. 163–186. North-Holland, Amsterdam.

HELLON R. F. (1967) Thermal stimulation of hypothalamic neurones in unanesthetized rabbits. *J. Physiol.* **193,** 381–395.

HELLON R. F. (1970) The stimulation of hypothalamic neurones by changes in ambient temperature. *Pflügers Arch. ges. Physiol.* **321,** 56–66.

HELLON R. F. (1972) Temperature-sensitive neurons in the brain stem: their responses to brain temperature at different ambient temperatures. *Pflügers Arch. ges. Physiol.* **335,** 323–334.

HELLON R. F. & MITCHELL D. (1975) Convergence in a thermal afferent pathway in the rat. *J. Physiol.* **248,** 359–376.

HELLON R. F., HENSEL H. & SHAFER K. (1975) Thermal receptors in the scrotum of the rat. *J. Physiol.* **248,** 349–357.

HENDLER E., HARDY J. D. & MURGATROYD D. (1963) Skin heating and temperature sensation produced by infrared and microwave irradiations. In *Temperature, Its Measurement and Control in Science and Industry*, III, Vol. 3, pp. 211–230. Reinhold, New York.

HENSEL H. (1952) Physiologie der thermoreception. *Ergeb. Physiol.* **47**, 166–368.

HENSEL H. (1974) Thermoreceptors. *Ann. Rev. Physiol.* **36**, 233–249.

HENSEL H. (1976) Functional and structural basis of thermoreception. *Prog. Brain Res.* **43**, 105–118.

HOREYSECK G., JANIZ W., KIRCHNER F. & THAMER V. (1976) Activation and inhibition of muscle and postganglionic neurones to hindlimb during hypothalamically induced vasoconstriction and atropine-sensitive vasodilation. *Pflügers Arch. ges. Physiol.* **361**, 231–240.

HOROWITZ J. M. & HORWITZ B. A. (1979) An overview of neural models postulated for thermoregulation. In *Body Temperature—Regulation, Drug Effects, and Therapeutic Implications* (Edited by LOMAX P. & SCHÖNBAUM E.), pp. 25–37. Marcel Dekker, New York.

IGGO A. (1969) Cutaneous thermoreceptors in primates and subprimates. *J. Physiol.* **200**, 403–430.

IGGO A. & YOUNG D. W. (1975) Cutaneous thermoreceptors and thermal nociceptors. In *The Somatosensory System* (Edited by KORNHUBER H. H.). Georg Thieme, Stuttgart.

IRIKI M., RIEDEL W. & SIMON E. (1977) Regional differentiation of sympathetic activity during hypothulamic heating and cooling in anesthetized rabbits. *Pflügers Arch. ges. Physiol.* **328**, 320–331.

JAHNS R. (1975) Types of neuronal responses in the rat thalamus to peripheral temperature changes. *Exp. Brain Res.* **23**, 157–166.

KEATINGE W. R. (1969) *Survival in Cold Water*. Blackwell Scientific, Oxford.

KRÖNERT H. & PLESCHKA K. (1976) Lingual blood flow and its hypothalamic control in the dog during panting. *Pflügers Arch. ges. Physiol.* **367**, 25–31.

LANDGREN S. (1957) Cortical reception of cold impulses from the tongue of the cat. *Acta physiol. scand.* **40**, 202–209.

LITTLE R. A., MARSHALL H. W., REYNOLDS M. I. & STONER H. B. (1980) Effect of changes in baroreceptor input on the intensity of shivering in the anesthetized cat. *Pflügers Arch. ges. Physiol.* **384**, 261–265.

LIU J. C. (1979) Tonic inhibition of thermoregulation in the decerebrate monkey (*Saumiri sciureus*). *Exp. Neurol.* **64**, 632–648.

MATHEW L., PURKAYASTHA S. S. & MALHORTRA M. S. (1978) Cold-induced vasodilation response at different water bath temperatures in monkeys. *Aviat. Space Environ. Med.* **49**, 976–974.

MCKEAN T. A., POPPELE R. E., ROSENTHAL N. P. & TERZUOLO C. A. (1970) The biologically relevant parameter in nerve impulse trains. *Kybernetik* **6**, 168–170.

MERCER J. B., JESSEN C. & PIERAU FR.-K. (1978) Thermal stimulation of neurons in the rostral brain stem of conscious goats. *J. therm. Biol.* **3**, 5–10.

MOTT J. C. (1963) The effects of baroreceptor and chemoreceptor stimulation on shivering. *J. Physiol.* **166**, 563–586.

NICOLAIDIS S. & SIVADJIAN J. (1972) High-frequency pulsatile discharge of human sweat glands: myoepithelial mechanism. *J. appl. Physiol.* **32**, 86–90.

OGAWA T. & ASYAMA M. (1978) Frequency of sweat expulsions, as indicator of sudomotor neural activity. In *New Trends in Thermal Physiology* (Edited by HOUDAS Y. & GUIEU J. D.). Proc. Sat. Symp. Thermal Regulation, pp. 105–107. Masson, Paris.

PERKEL D. H. & BULLOCK T. H. (1968) Neural coding. *Neurosci. Res. Prog. Bull.* **6**, 221–348.

PERKEL D. H. & MULLONEY B. (1974) Motor pattern production in reciprocally inhibitory neurons exhibiting postinhibitory rebound. *Science* **185**, 181–183.

PERKINS J. F. (1945) The role of the proprioceptors in shivering. *Am. J. Physiol.* **145**, 264–271.

PIERAU F., TORREY P. & CARPENTER D. O. (1975) Afferent nerve fiber activity responding to temperature changes of scrotal skin of the rat. *J. Neurophysiol.* **38**, 601–612.

PREISS G. & POLOSA C. (1974) Patterns of sympathetic neuron activity associated with mayer waves. *Am. J. Physiol.* **226**, 724–730.

POULOS D. A. (1975) Central processing of peripheral temperature information. In *The Somatosensory System* (Edited by KORNHUBER H. H.), pp. 78–93. Georg Thieme, Stuttgart.

RANDALL W. C. & HERTZMAN A. B. (1953) Dermatomal recruitment of sweating. *J. appl. Physiol.* **5**, 399–409.

REAVES T. A. & HEATH J. E. (1975) Interval coding of temperature by CNS neurones in thermoregulation. *Nature* **257**, 688–690.

REAVES T. A. (1976) Thermosensitive characteristics of preoptic area neurons in the New Zealand white rabbit, *Oryctolagus cuniculus*. Ph.D. Dissertation, University of Illinois, Urbana.

REAVES T. A. & HAYWARD J. N. (1979) Hypothalamic and extrahypothalamic thermoregulatory centers. In *Body Temperature—Regulation, Drug Effects and Therapeutic Implications* (Edited by LOMAX P. & SCHONBAUM E.), pp. 39–70. Marcel Dekker, New York.

SATINOFF E. (1978) Neural organizational and evolution of thermal regulation in mammals. *Science* **201**, 16–22.

SCHINGNITZ G. & WERNER J. (1980) Thalamic burst firing—a neuronal code for temperature information? *Brain Res.* **195**, 467–470.

SCHWINGHAMER J. M. & ADAMS T. (1969) Cold-induced vasodilation in the footpad of the anesthetized cat. *Fedn Proc. Fedn Am. Socs exp. Biol.* **28**, 1149–1153.

SEGUNDO J. P., MOORE G. P., STENSAAS L. J. & BULLOCK T. H. (1963) Sensitivity of neurones in *Apylsia* to temporal pattern of arriving impulses. *J. exp. Biol.* **40**, 643–667.

SIMON E. (1974) Temperature regulation: the spinal cord as a site of extrahypothalamic thermoregulatory functions. *Rev. Physiol. Biochem. Pharmacol.* **71**, 1–76.

STUART D. G., ELDRED E., HEMINGWAY A. & KAWAMURA Y. (1963) Neural regulation of the rhythm of shivering. In *Temperature, its Measurement and Control in Science and Industry*, III, Vol. 3, pp. 545–557. Reinhold, New York.

STUART D. G., ELDRED E., HEMINGWAY A. & KAWAMURA Y. (1966) The rhythm of shivering. I. general sensory contributions. *Am. J. Phys. Med.* **45**, 61–74.

TERZUOLO C. A. & BAYLY E. J. (1968) Data transmission between neurons. *Kybernetik* **5**, 83–85.

UEDU G. (1978) Vasomotor thermoregulation under local cold stress. In *New Trends in Thermal Physiology* (Edited by HOUDAS Y. & GUIEU J. D.). Proc. Sat. Symp. Thermal Regulation, pp. 127–129. Masson, Paris.

VON EULER C. (1950) Slow "temperature potentials" in the hypothalamus. *J. cell comp. Physiol.* **36**, 333–350.

VON EULER C. & SODERBERG U. (1957) The influence of hypothalamic thermoreceptive structures on the electroencephalogram and gamma motor activity. *EEG & Clin. Neurophys.* **9**, 341–408.

WALTHER O., IRIKI M. & SIMON E. (1970) Antagonistic changes of blood flow and sympathetic activity in different vascular beds following central thermal stimulation. *Pflügers Arch. ges. Physiol.* **319**, 162–184.

WERNER G. & MOUNTCASTLE V. B. (1963) The variability of central neural activity in a sensory system and its implications for the central reflection of sensory events. *J. Neurophysiol.* **26**, 958–977.

WHITSEL B. L., SCHREINER R. C. & ESSICK G. K. (1977) An analysis of variability in somatosensory cortical neuron discharge. *J. Neurophysiol.* **40**, 589–607.

WIEDERHIELM C. A. (1966) Effects of temperature and transmural pressure on contractile activity of vascular smooth muscle. In *Fourth European Conf. on Microcirculation* (Edited by HARDERS H.), pp. 321–327. Karger, Basel.

WIERSMA C. A. & ADAMS R. T. (1950) The influence of nerve impulse sequence on the contractions of different crustacean muscles. *Physiol. Comp.* **2,** 20–33.

WILSON H. C. (1936) The relation between rhythmic variations in blood pressure and rhythmic contractions of the artery of the rear of rabbits and dogs. *Am. J. Physiol.* **116,** 295–301.

WÜNNENBERG W. (1973) Alteration of EEG activity of the hypothalamus by thermal stimulation of the spinal cord. *Pflügers Arch. ges. Physiol.* **344,** 75–82.